

Die Erfindung betrifft eine mikrosystemtechnische Vorrichtung zur DNA-Amplifizierung mit Hilfe der Polymerase-Kettenreaktion (PCR), mit einem ersten Wafer und einem mit dem ersten Wafer sandwichartig verbundenen zweiten Wafer, einer Reaktionskammer zwischen den Wafern, mindestens einem in die Reaktionskammer mündenden, eintragenden Kanal und einem von der Reaktionskammer abgehenden, austragenden Kanal, und einer Heizvorrichtung zum Aufheizen und einer Kühlvorrichtung zum Abkühlen der Reaktionskammer.

Such devices for the duplication of a specific DNA section between two defined pairs of nucleotides of a gene with the help of the polymerase nuclear chain reaction (polymerase chain reaction, PCR) are well-known. The PCR becomes increasingly important since center of the 80's inserted with the recognition of genetically caused diseases, to research purposes or the identification of micro organisms. For this well-known-measured the exit DNA with the DNA section, which can be multiplied available in aqueous solution, into a reactor brought. By heating the sample solution up in the reactor on approx. The doppelstrangige DNA Helix splits 95 DEG up C into two single strands. After this so-called. To denature an artificially synthesized knows and the aqueous solution in sufficient quantity added, specific DNA piece of small number of cousins at an end of the too amplifizierenden DNA section single strand (so-called. Primers) bind. At the other end of the too amplifizierenden DNA section of the complementary single strand another specific primer binds. The place of the connection of the two primers limits the too amplifizierenden DNA section. These so-called. Hybridizing runs off optimal at temperatures of approximately 45 DEG C, D. h. that the sample volume must after isolating the DNA of gleaning rank cooling. At the available two single strands with its respective bound primers the so-called becomes with the help of a initially added, heat-stable enzyme. Taq polymerase, successively - beginning with each other turned primer ends - also to onset added nucleotides added. This as synthesis designated procedure runs off fastest with approximately 72 DEG C, why the sample volume in the reactor must be warmed up after hybridizing the primers again. At the end of this Zyklus' one receives thus two doppelstrangige DNA molecules, which both exhibit the DNA section which can be multiplied. Are implemented several times one behind the other the cycle doubling in each case from denaturing, hybridizing and synthesizing if existing and the DNA section, one receives an approximately billionfold copy number of the too amplifizierenden DNA section with a Zykluszahl according to standard from 30. This is sufficient, in order to be able to use afterwards well-known methods of analysis. During some these analysis reactions in few minutes to be run off and evaluated, take into most well-known devices know the accomplished PCR some hours and limit the timed throughput by the devices.

Due to the versatility of the PCR - to call are here in particular the multiplex PCR and in particular the so-called. Fingerprinting method - are lately attempts admits become to reduce with the help of micro-system-oriented devices the cycle times on few minutes in order to make thereby fast gene analyses possible, for example during operations. Special attention applies well-known for micro-system-oriented devices and here in particular the reduction of the sample chamber volume, since then the heating and cooling times of the sample solution must amount to only few seconds. Dies ist ausreichend, damit die drei verschiedenen Reaktionen innerhalb eines

PCR- Zyklus' ablaufen, So ist beispielsweise eine Vorrichtung bekannt, bei der zwei Wafer übereinander angeordnet sind, zwischen denen eine Reaktionskammer durch eine Aussparung auf der Innenseite eines aus einem Halbleitermaterial bestehenden Wafers ausgebildet ist. The other one, the recess taking off wafer covers heating element with this well-known device.

With this well-known device in particular of them are unfavorable verhältnismässig unfavorable thermal characteristics. Since for the reduction of the cycle times the volume of the reactor is small as selected as possible, the depth of the recess is relatively small compared with the usually standardized overall thickness of the wafer. This again means that over the space-seizing environment sections of the reactor warmth flows off, which does not stand for the heating up/cooling of the sample solution for order. The relatively large thermal mass of the environment sections of the reactor resulted thus in unfavorably long heating and cooling times of the sample volume.

Further the DNA amplifizierte in the reactor is if necessary from the remaining substances with this well-known device unfavorably that the following analysis of the amplifizierten DNA cannot be accomplished in all cases immediately, there depending upon methods of analysis (and. A. Buffer, surplus primer and nucleotides, Taq polymerase, activators) separate will must. For example the well-known matrix-supported flying time mass spectrometry (MALDI TOF ms requires: matrix assisted laser desorption time OF flight measured spectrometry) a relatively highly concentrated DNA solution. The intermediate step of the Aufreinigung is relatively to the cleaning device however difficult because of the transport of the DNA molecules from the reactor to accomplish.

Task of the present invention is it to train the micro-system-oriented device further of the kind initially specified in such a manner that the period can be reduced in a simple manner by the onset of a PCR up to the DNA analysis.

This task is solved with the micro-system-oriented device of the kind initially specified according to invention by the fact that first and/or the second wafer in the region of the reactor exhibit a recess on its exterior.

Furthermore the invention with the micro-system-oriented device of the kind initially specified solved by a cleaning chamber between the two Wafers to the Aufreinigung of the amplifizierten DNA molecules, at least, a registering channel, which are connected with a delivering channel of the reactor, flowing into the cleaning chamber, and at least, delivering channel a going off the cleaning chamber.

The advantages of the reactor according to invention are in particular in the fact that or both wafer a recess on the exterior exhibit, which is in the region of the reactor disposed. The depth of the recess on the exterior or the wafer determines the wafer thickness between the reactor and the outside recess. With desired a small-volumed and accordingly flat reactor the recess on the wafer exterior can be in such a manner deeply trained that that and/or. the wafer in the region of the reactor a very small thickness exhibit. Thereby the thermal mass of these wafer sections becomes very small, since only over narrow space bridges contact with the more distant wafer sections exists and is thus derived during the heating and cooling phases only slightly warmth to these.

The thermal capacity that the reactor of neighbouring wafer sections is reduced thus according to invention and it to result faster temperature rises as well as - abfälle in the reactor, if the reactor is heated or cooled down. Thereby PCR cycle times of less than five seconds can be realized with a chamber volume of approximately 1 μ l, so that a PCR with 30 cycles can be accomplished in less than three minutes.

The advantages of the cleaning chamber integrated together with the reactor between two Wafers are to be in particular seen therein that the amplifizierten DNA molecules directly following the PCR over a connecting duct to the cleaning chamber can be led, in which the amplifizierte DNA up-cleaned become. At the exit of the cleaning chamber up-cleaned DNA will thus receive, which must be brought in only still in an analysis device. In particular with the multiplex PCR, with which at the same time different pairs of primers are admitted to the Amplifizierung of different DNA sections of the reaction solution, the integration according to invention of reactor and cleaning chamber between two Wafers accelerates the massenspektrometrische analysis with bspw. dem MALDI-Verfahren, die - im Gegensatz zu einer Gelelektrophorese - den Vorteil besitzt, dass DNA-Fragmente sehr unterschiedlicher Grösse gleichzeitig bestimmbar sind. To the preparation of the device according to invention conventional are applicable wet and drying-chemical etching techniques as well as well-known photolithographic methods. Furthermore exists the favourable possibility, the so-called. To use batch procedure, with which the structures first and the second wafer can be manufactured at the same time in each case in high number on large wafer disks. The afterwards adjacent large wafer disks need to become then only slightly processed, in order to receive numerous devices according to invention. Particularly preferentially the cavity of the reactor according to invention is formed by interiorlateral recesses in the first and/or second wafer. In similar way interiorlateral recesses in the first and/or second wafer are leading to the formation of to the reactor and if necessary. intended by the reactor continuing channels.

Over as even a heating up as possible and/or. Cooling of the sample volume in the reactor to receive, essentially extends in a particularly preferred embodiment the outside recess over the entire surface of the reactor projected to the exterior.

Particularly preferentially the reactor exhibits an essentially oblong form, in order to avoid a mixing of the PCR products when washing out with a rinsing solution, as for example water. The PCR products are pressed here by the following rinsing solution from the reactor and are present therefore at their exit essentially in undiluted form.

Preferred the heating device needed for the heating of the sample volume covers at least an electrical isolated heating conductor in the reactor. For example the heating conductor is disposed over the entire surface of the reactor projected to the exterior in form of a Mäanders, in order to as evenly and warm up the solution in the reactor fast as possible. With this embodiment is the solution which can be warmed up favourable-proves - compared with a heating device disposed on the wafer exterior - in direct proximity of the heating conductor. Thereby a time-consuming indirect heating up of the sample solution is avoided due to a before necessary heating up of the wafer.

If that is made of a semiconductor material the heating conductor neighbouring wafer, the heating conductor is preferentially into an electrical isolating layer in the reactor embedded for the avoidance of short-circuits, in order to isolate the heating conductor in this way against the semiconductor material and the conductive PCR solution. To the realization can be fallen back to well-known microstructure procedures.

A fast cooling of the sample solution in the reactor can be obtained, if the cooling device at least one nozzle enclosure, which is directed toward the outside wafer surface in the region of the recess, over over convection warmth abzutransportieren. Favourable way is directed a nozzle toward that the heating conductor neighbouring wafer section, so that after interrupting the filament current the remainder warmth of the heating conductor can be exhausted fast.

In a preferential further training of the invention are cooling fins in that and/or. the recesses on the wafer exteriors disposed, which exhibit a relatively large surface for the support of the Konvektionskühlung.

Particularly preferentially upstream the reactor several channels between the two Wafern are disposed, which serve the supply of DNA solutions, reaction solutions and/or rinsing solutions. Thereby the concentrations as well as the timed succession of the supply of the individual solutions can become adjusted.

Favourable way the reaction solutions supplied by at least two channels are led before entrance into the reactor by a mixing apparatus, so that the reaction of the molecules of the different liquids in the reactor is accelerated.

Particularly preferentially pneumatically operated valves and/or pumps are integrated in the array both the wafer, which serve for the passage adjustment of the channels. The integration of the preferably individually controllable valves into the wafer arrangement contributes with at the same time simple management to the miniaturization of the device according to invention.

Eine besonders bevorzugte Ausführungsform sieht vor, dass die inneren Oberflächen der Reaktionskammer sowie ggf. the channels for the avoidance of reciprocal effects also in the solutions suspended molecules are chemically inertisiert. In this way it is ensured that the PCR is not disturbed by reactions at the internal surfaces of the reactor. For example the chamber surfaces are provided with actually well-known coatings - for example organic molecules -.

The cavity together according to invention with the reactor between two Wafern integrated cleaning chamber is preferentially by interiorlateral recesses in the first and/or second wafer formed. In similar way interiorlateral recesses in the first and/or second wafer are leading to the formation of to the cleaning chamber and if necessary. intended by the cleaning chamber continuing channels.

The DNA molecules amplifizierten in the reactor are up cleanable after transport to the cleaning chamber by means of an actually well-known separate ion technology. It is offered to z. B. on to deposit to with the PCR of inserted primer molecules in front in each case a Biotin or a Avidin molecule so that at the end of the PCR each amplifizierte DNA molecule a Biotin and/or. Avidin group exhibits. With employment of this method the device according to invention exhibits preferably one upstream the cleaning chamber disposed channel for the supply of a suspension of

magnetic particles, to which at least in each case one Streptavidin group is angelagert. In the cleaning chamber then the Streptavidin groups of the magnetic particles can bind at the Biotin or Avidin groups of the primer sequences of the DNA molecules under education of a relatively large, magnetic complex.

To the Separation of the remaining, while the PCR necessary molecules is at least one magnet in the region of the cleaning chamber intended, which immobilizes the magnetic complexes due to magnetic attraction in the cleaning chamber, while the remaining molecules with the solution from the cleaning chamber are delivered.

In an alternative embodiment for separation and/or. Aufreinigung of the amplifizierten DNA molecules are occupied the surfaces of the cleaning chamber with Streptavidin groups, to which the Biotin or Avidin groups of the primer sequences of the amplifizierten DNA molecules binds. In this case the DNA of molecules of the remaining molecules in the solution on purely chemical way - without use of outside fields externally put on - becomes separate.

Over at the Streptavidin groups of the magnetic particles and/or. the surfaces of the cleaning chamber adhering DNA molecules to separate, is upstream the cleaning chamber a channel for the supply of a Elutionslösung and/or. - buffers intended, in that itself the immobilized DNA molecules - if necessary. nach Abschaltung des magnetischen Feldes - lösen, um anschliessend aus der Reinigungskammer ausgetragen zu werden.

Particularly preferentially an embodiment of the device according to invention exhibits a heating device in the cleaning chamber, which favourable-proves essentially the same structure as the heating device of the reactor described above possesses. The heating device provides for an optimal temperature in the cleaning chamber, with which the magnetic particles with increased Reaktionsgeschwindigkeit prefers at the DNA molecules bind and at the same time the number of nonspecific connections is reduced. Also a cooling device can be intended in the region of the cleaning chamber, which essentially corresponds to the cooling device for the reactor, described above. For the passage adjustment of the channels it offers itself further, pneumatically operated valves and/or pumps for the supply and/or. Derivative from solutions to and/or. to use from the cleaning chamber.

Favourable way exhibits first and/or the second wafer in the region of the cleaning chamber a recess on its exterior, there thereby - as in case of the recess (EN) in the region of the reactor - a fast call heating of the sample solution in the cleaning chamber is favoured. The recess in the region of the cleaning chamber reduces here likewise the heat discharge into more distant wafer sections.

A piezoelectric pump is particularly preferential in a delivering channel of the cleaning chamber disposed, with which accurate defined drops into the Elutionslösung loosened amplifizierten DNA molecules in concentrated form are orderable on a relatively small surface. This is particularly with an analysis of the amplifizierten DNA - if necessary. with the magnetic particles still bound at the DNA molecules - by means of the MALDI method for this a small, as evenly as possible also layer covered to analyzing sample molecules is favourable favourably, there. Therefore the sample volume needed for the mass spectrometry can and thus if necessary with the

help of the piezoelectric pump. the quantity to necessary exit DNA and/or. the number of PCR cycles which can be accomplished to be reduced.

If two channels gather, which successively different solutions lead into a common channel, it is desirable that as small a dead volumes in the channel arms as possible develop, which could lead to contamination due to for example deposits. In particular a liquid critical in this regard, which is supplied by way of a first channel, is to be as completely as possible carried forward effectively by one afterwards over a second channel supplied rinsing solution, without parts of the critical liquid in the duct system stay. For this purpose a micro-system-oriented device with a first wafer and with the first wafer sand yield-like connected a second wafer is suggested, as well as with interiorlateral recesses in the first and/or second wafer for the education by channels between the two Wafern. At least one valve is in the region of the Zusammenlaufs of a first channel and a second channel intended to a third channel according to invention. The valve contains as flexible layer of the first or second wafer a trained diaphragm, which forms a flexible extent section of the wall of the first channel, whereby the flexible extent section in closing position of the valve puts on itself against a opposite firm extent section of the wall of the first channel and stands out in Offenstellung of the valve against the firm extent section.

If liquid is led by the first channel to the open valve, flows this between the diaphragm forming a flexible extent section of the first channel and the firm extent section into the third channel and concomitantly into the second channel, which flows in direct proximity to the valve into the third channel. With latches of the valve the flexible diaphragm sets itself sealing on the firm extent section of the first channel and prevents the liquid flow. Wird nach Schliessen des Ventils Spüllösung über den zweiten Kanal zugeführt, nimmt die Spüllösung Flüssigkeit in den dritten Kanal mit, welche zuvor bei offenem Ventil in den zweiten Kanal geströmt ist bzw. still in the region of the closed valve is. Means of this array no dead arms for the liquid and it develop depositing critical liquid components are in a simple manner avoided during the rinsing procedure.

Particularly preferentially the firm extent section exhibits a collection of the first or second wafer between the recesses for the first channel on the one hand and for the second and third channel on the other hand, at which the diaphragm comes into closing position of the valve sealing to the plant. Such a collection can be received in simple way by applying appropriate masks during the etching process steps.

Favourable way is intended a pressure chamber on the channel-turned away side of the diaphragm. If the pressure chamber with positive pressure is subjected, the diaphragm puts to the firm extent section. If however a vacuum in the pressure chamber is produced, the diaphragm stands out against the firm extent section and releases the river of the first channel in third and also into the second channel.

Preferred a lidding foil takes the pressure chamber off on the diaphragm facing the side. The lidding foil exhibits favourable-proves an opening for the connection of a sucking and/or a pressure pump. Alternatively the pressure chamber is covered with a continuous resilient foil and can be subjected by means of an external - for example mechanical - pressure surge on the

resilient foil with pressure.

Favourable training further of the invention are characterized by the features of the Unteransprüche.

In the following an embodiment of the invention is more near described on the basis the designs. Show:

Fig. 1 a schematic representation of a micro-system-oriented device with a reactor and a cleaning chamber as well as different channels;

Fig. 2 a supervision on an embodiment of the device in accordance with the pattern of the Fig. 1 with widened duct system;

Fig. 3 a cross section along the line A-A by the wafer arrangement of the Fig. 2;

Fig. 4 an increased representation of the valve of the Fig. 3 in Schliessstellung;

Fig. 5 an increased representation of the valve of the Fig. 3 in Offenstellung;

Fig. 6 a valve in the region of two approaching channels and a channel running off in closing position; and

Fig. 7 in accordance with valve the Fig. 6 in Offenstellung.

In Fig. 1 is schematically a micro-system-oriented device 1 with a reactor 6 represented to 8 DNA molecules amplifizierten to the Aufreinigung during the PCR for the execution of a PCR and a cleaning chamber. As from Fig. 3, is angordnet the two chambers 6, 8 between a first wafer 2 and a second wafer 4, those comes out by means of well-known sticking or welding processes, like z. B. that so-called. Waferbonding, are laminar connected. The two wafer 2, 4 are as for example silicon manufactured from a semiconductor material. Alternativ können z. B. also glass or polymere plastics or other suitable plastics to be used.

Like further the Fig. 1 to infer is, leads a registering channel 40 to the reactor 6. Upstream two further channels 46, 49 into the channel 40, which exhibit in each case inlet ports 56, 59 for the supply of exit DNA, other reagents as well as rinsing solutions necessary for the PCR, flow. At the knot of the channels 46, 49 and 40 a valve is 50 disposed for passage adjustment.

The reactor 6 a delivering channel 42 goes off, which is connected by a valve 60 with, a registering channel 70 flowing into the Reingigungskammer 8. In the cleaning chamber 8 become in the reactor the 6 amplifizierten, still in the reaction solution suspended DNA molecules of the remaining molecules of the reaction solution separate. For this a further registering channel 71 into the cleaning chamber 8, into which upstream two further, over a valve 80 controlled channels 76, 77 flows, over inlet ports cleaning, Elutions flows to those as well as if necessary. Rinsing solutions are supplyable. A delivering, valve-controlled channel 72 leads from the cleaning chamber 8 to an outlet opening 99 of the device 1.

The cavities of the oblong, parallel inner walls in pairs exhibiting reactor 6 as well as the cleaning chamber 8 essentially rechteckförmigen in the supervision are by recesses on the inside of the upper, first wafer 2 and the lower, second wafer 4 (in each case related to Fig. 3) formed. The cavities of the registering and/or. delivering channels 40, 42, 70, 72 - as well as the remaining channels - are formed in the represented embodiment by interiorlateral recesses in the second wafer 4 (S. Fig. 3).

Like in particular from the Fig. 3 comes out, is on the exterior of the two wafer 2, 4 in the region of the reactor 6 in each case a recess 10, 12 intended, which are to each other mirror-symmetrically as one essentially by the boundary surface both wafer 2, 4 running level trained. The two outside recesses 10, 12 taper themselves both lengthwise-laterally and at the front side to the reactor 6 and extend in the region of the reactor 6 over their entire surface projected to the exterior. The wafer thickness in this region is very small compared with the neighbouring wafer sections, in order to keep the heat discharge small to these sections. The profile of the reactor 6 can exhibit different forms depending upon used etching technique alternatively also.

In the upper region of the reactor 6 (Fig referred. 3) a heating conductor 23 embedded from for example aluminum in an electrical isolating layer 20 is out for example silicon dioxide. The heating conductor 23 runs mäanderförmig from a front side of the reactor 6 on the other hand and is at its two free ends in each case over z. B. on the wafer evaporated connecting lines 25 to connection contacts 24 led (Fig. 2).

A nozzle 36 in the region of the recess 10 of the first wafer 2 is directed toward the wafer surface in the region of the reactor 6 and serves for the Konvektionskühlung of a sample solution in the reactor 6. In der Aussparung 10 sind hintereinander konstant beabstandete Kühlrippen 37 über die gesamte Länge der Reaktionskammer 6 zur Unterstützung des Konvektionsprozesses angeordnet. At the left contour of the Fig. the inlet port 56 of the channel 46 flowing into the channel 40 is represented 3. The inlet port 56 - like if necessary. also the remaining inlet ports - is for example trained as pyramid-shaped breaking through in the first wafer 2, whose approaching end meets right-angled the channel 46. The exterior of breaking through is covered with a lidding foil 94 from for example plastic, which exhibits an opening 96 for attaching a supplying hose (not represented).

In Fig. 3 and in enlargement in the Fig. 4 and 5 represented valve 60 regulates the river of the reactor 6 over the channels 42, 70 to the cleaning chamber 8. The valve 60 exhibits a pressure chamber 93 with itself to the boundary surface both wafer 2, 4 the tapering cross section. The pressure chamber 93 is limited externallaterally by lidding foil 94 a resting upon the exterior of the first wafer 2, whatever for example the inlet port 56 (Fig. 3) and the remaining inlet ports covers. The lidding foil 94 points an opening 96 up, at which for example a sucking and/or a pressure pump (not represented) are connectable, over the pressure in the pressure chamber 93 to increase and/or. to degrade. The lidding foil 94 opposite is a wafer section disposed, which as thin diaphragm 95 is designed and represents a flexible extent section of the channels 40, 72. During application of pressure of the pressure chamber or with ambient air pressure the diaphragm sets itself 93 on a collection 97, which separates the recesses for the two channels 42, 70. With reduction in pressure or vacuum in the pressure chamber 93 the diaphragm 95 (Fig lifts itself. 5) and the connection between the channels releases 42, 70.

The first wafer 2 has an outside recess 14, whose form essentially resembles the recess 10 in the region of the reactor 6 in the region of the cleaning chamber 8. The cleaning chamber 8 exhibits likewise - analogue to the appropriate elements reactor 6 - in an electrical insulative layer 26 embedded heating conductor 27 and appropriate connecting lines 29 to connection contacts 28 on

the first wafer 2.

On the exterior of the second wafer 4 an electromagnet coil is 98 disposed in the region of the cleaning chamber 8, which is integrated for example in an surface-installed construction unit (surface mounted DEVICES) and is not attached not represented feed lines on. With current flow by the solenoid coil 98 an inhomogenous magnetic field in the cleaning chamber 8 is produced. In Fig. 2 represented embodiment points - in extension of the schematic representation of the Fig. 1 - a widened duct system disposed between the two Wafern 2, 4 upstream the reactor 6 up. Additionally to the inlet port 56 for the exit DNA and the inlet port 59 for a rinsing solution, as for example water or a glycine/a HCl buffer, a separate inlet port 58 for intended to the PCR the few reagents is. Preferably computer-controlled valves 50-52 are 46-49 disposed for the passage adjustment of the individual solutions in the channels leading to the channel 40. A controllable mixing apparatus 45 in the registering channel 40 between the reactor 6 and the upstream nearest valve 50 serves for the optional mixing of solutions, which are supplied at the same time or successively by means of the channels 46-49. Between the mixing apparatus 45 and the reactor 6 additionally a not represented valve can be intended, which lets only mixed solutions happen if necessary to the reactor 6.

In similar way is the cleaning chamber 8 a widened duct system with several - in the embodiment in accordance with the Fig. 2 three - separate inlet ports 84-86 upstream. By the inlet port 84 for example a suspension of magnetic particles is supplyable by way of the channels 74, 77, 71 of the cleaning chamber 8. At the magnetic particles Streptavidin groups are preferably angelagert, which bind in the cleaning chamber at Biotin or Avidin groups, which are angelagert at the primer sequences of the amplifizierten DNA molecules. If the reactor 6 becomes leaving solution, which contains the amplifizierten DNA molecules as well as the remaining, the PCR of supporting reagents as well as buffer and activator molecules, with magnetic field of the solenoid coil 98 by the cleaning chamber, turned on at the same time, 8 led, the magnetic particles with at these bound DNA molecules in the cleaning chamber the 8 are held back, while the others, non-magnetic molecules are rinsed out. In the following a Elutionslösung can be led into the cleaning chamber 8 by the inlet port 86 of the channel 76 and over the channel 71, which - with now preferably switched off magnetic field - remains a given time in the cleaning chamber 8 and which from each other solves magnetic particle and the DNA molecules adherent to it. Preferably the magnetic field becomes only the Separation of the DNA molecules of the magnetic particles deenergized. Before recovery of the DNA sections the magnetic field is again activated, so that the magnetic particles become as not as possible with the DNA sections expenditure for. A third inlet port 85 to the supply of a rinsing solution, as for example water or a glycine/a HCl buffer, is connected by the channels 75, 77, 71 likewise with the cleaning chamber 8. The supply by those differently channels to the cleaning chamber 8 is regulated by controllable valves 80-82.

Into the Fig. 6 and 7 represented valve 80 - just like the valves 50, 51, 82 - differs from in the Fig. 4 and 5 valve shown in the fact 60 essentially that two approaching channels 76, 77 flow in direct proximity of the valve 80 into a channel running off 71. The channel 77, that in the Fig. 6 and 7 perpendicularly to the indication level, is permanently with the channel 71 connected and not by

means of the valve 80 runs adjustable. However a collection is 97 disposed in the channel 76 directly upstream the delta into the channel 71, which in the second wafer 4 is trained and forms a firm extent section of the channel 76. In closing position of the valve 80 lies - the analogue valve 60 the Fig. 4 and 5 - a flexible diaphragm 95 on the collection 97, which is designed as thin layer of the second wafer 2 and a flexible extent section of the channel 76 and likewise the channels 77, 71 forms. In Offenstellung the diaphragm stands out 95 against the collection 97 and lets by the channel 76 supplied Elutionslösung into the channel 71 and also into the channel 77 flow. For the Ventilbetätigung, similarly, a pressure chamber 93 above the diaphragm 95 subjectable with pressure serves the valve 60 (related to the Fig. 6 and 7). Elutionslösung, which flows with closed valves 81, 82 into the channel 77, is innocuous, since - after latches of the valve 80 - over the inlet 85 admitted rinsing solution carries these small quantities and over the channel 71 to the cleaning chamber 8 and from there out passes on. In this way the Elutionslösung is delivered by means of the rinsing solution completely from the device 1. Arrears of the Elutionslösung cannot settle. In same way z becomes. B. by means of the valve it ensures 50 that over the channel 46 supplied exit DNA completely into the reactor 6 arrives.

If necessary the valves 50, 51, 80, 82 point an additional diaphragm as well as an additional, to separately subjectable pressure chamber for regulation also the other approaching channel to (not represented).

In Fig. 2 represented embodiment is two the cleaning chamber of 8 leaving channels 72, 73 intended, which are controllable in each case over a valve 88, 89. Delivering channel the 73 flows into a waste discharge opening 87, by which one by the cleaning chamber 8 and if necessary. by the reactor 6 led rinsing solution is exhausted. The other, channel 72 serving for delivering the amplifizierten DNA molecules a piezoelectric pump is inserted 90, which lays into the Elutionslösung loosened DNA molecules by the discharge opening 99 concentrated for example on a thin layer 100 on, which with a following measure-spectrometric DNA regulation by ionization with matrix-supported laser desorption in a flying time mass spectrometer in well-known way is more useful.

Claims:

1. Micro-system-oriented device (1) to the DNA Amplifizierung with the help of the polymerase nuclear chain reaction (PCR), also
a first wafer (2) and one with the first wafer (2) sand yield-like connected second wafer (4),
a reactor (6) between the Wafern (2, 4),
at least one into the reactor (6) flowing, registering channel (40)
and one of the reactor (6) outgoing, delivering channel (42), and
a heating device (23, 24, 25) to heating and a cooling device (36, 37) for the cooling of the reactor (6),
characterised in that first and/or the second wafer (2, 4) in the region of the reactor (6) a recess (10, 12) on its exterior exhibits.
2. Device according to claim 1, characterised in that interiorlateral recesses in the first and/or

second wafer (2, 4) the cavity of the reactor (6) form.

3. Device according to claim 1 or 2, characterized by interiorlateral recesses in the first and/or second wafer (2, 4) to the formation of to the reactor (6) leading and if necessary. of the reactor (6) continuing channels (40, 42, 46-48).

4. Device after one of of the preceding claims, characterised in that itself the externallateral recess (EN) (10, 12) essentially extended over the entire projected surface of the reactor (6), to the exterior.

5. Device after one of the preceding claims, characterised in that the heating device (23, 24, 25) at least a heating conductor (23) covers, which in the reactor (6) disposed is.

6. Device according to claim 5, characterised in that of the heating conductor (23) in an electrical isolating layer (20) in the reactor (6) is embedded.

7. Device after one of the preceding claims, characterised in that the cooling device (36, 37) one or more nozzles (36) in the region of the externallateral recess (EN) (10, 12) covered for the Konvektionskühlung of the wafer surface.

8. Device after one of the preceding claims, characterised in that the cooling device (36, 37) cooling fins (37) in/the externallateral recess (EN) (10, 12) covered.

9. Device after one of the preceding claims, characterized by upstream the reactor (6) disposed channels (46-49) to the supply of DNA solutions, reaction solutions and/or rinsing solutions.

10. Device according to claim 9, characterised in that a mixing apparatus (45) in a registering channel (40) disposed is, into which upstream at least two channels (46-49) flow to the mixing apparatus (45).

11. Device after one of the preceding claims, characterised in that pneumatically operated valves (50, 51, 52) and/or pumps for the passage adjustment of the channels (40, 42, 46-49) into the array the wafer (2, 4) are integrated.

12. Device after one of the preceding claims, characterised in that the internal surfaces of the reactor (6) as well as if necessary. the channels (40, 42, 46-49) for the avoidance of reciprocal effects also in the solutions suspended molecules are inertisiert.

13. Mikrosystemtechnische Vorrichtung, insbesondere nach einem der Ansprüche 1 bis 12, welche zwei sandwichartig verbundene erste und zweite Wafer (2, 4) und eine Reaktionskammer (6) zur DNA-Amplifizierung mittels einer PCR-Reaktion zwischen den Wafern (2, 4) umfasst, gekennzeichnet durch eine Reinigungskammer (8) zwischen den beiden Wafern (2, 4) zur Aufreinigung der amplifizierten DNA-Moleküle, mindestens einen in die Reinigungskammer (8) mündenden, eintragenden Kanal (70), der mit einem austragenden Kanal (42) der Reaktionskammer (6) verbunden ist, und mindestens einen von der Reinigungskammer (8) abgehenden, austragenden Kanal (72, 73).

14. Device according to claim 13, characterised in that interiorlateral recesses in the first and/or second wafer (2, 4) the cavity of the cleaning chamber (8) form.

15. Device according to claim 13 or 14, characterized by interiorlateral recesses in the first and/or second wafer (2, 4) to the formation of to the cleaning chamber (8) leading and/or. of the cleaning chamber (8) continuing channels (70-77).

16. Device after one of the claims 13 to 15, characterized channel (74), disposed by one upstream the cleaning chamber (8), for the supply of a suspension of magnetic particles, which angelagerte Streptavidin groups exhibit for connection at Biotin or Avidin groups, which at primer sequences of a amplifizierten DNA molecule are angelagert.
17. Device according to claim 16, characterized by at least one magnet (98) in the region of the cleaning chamber (8) to the immobilization of the DNA molecules adherent at the magnetic particles.
18. Device after one of the claims 13 to 17, characterised in that the surfaces of the cleaning chamber (8) are to a large extent durably with Streptavidin groups occupied, to which in each case at primer sequences of a amplifizierten DNA molecule angelagerte Biotin or Avidin groups binds.
19. Device after one of the claims 13 to 18, characterized by upstream the cleaning chamber (8) disposed channels (71, 75-77) to the supply from Elutionslösungen to the separation of the DNA molecules from the particles exhibiting the Streptavidin groups and/or. Chamber surfaces and/or for the supply from rinsing solutions to the flushing of the cleaning chamber (8).
20. Device after one of the claims 13 to 19, characterized by a heating device (27, 28, 29), in particular as in the claims 5 and 6 described, and/or a cooling device, in particular as in the claims 7 and 8 described, in the region of the cleaning chamber (8) as well as pneumatically operated valves, in particular as in claim 12 described, and/or pumps for the passage adjustment of the channels (70-77).
21. Device after one of the claims 13 to 20, characterised in that first and/or the second wafer (2, 4) in the region of the cleaning chamber (8) a recess (14) on its exterior exhibits.
22. Device after one of the claims 13 to 21, characterized by a piezoelectric pump (90) in a delivering channel (72) of the cleaning chamber (8).
23. Micro-system-oriented device (1), in particular after one of the claims 1 to 22, also a first wafer (2) and one with the first wafer (2) sand yield-like connected second wafer (4), and with interiorlateral recesses in the first and/or second wafer (2, 4) to the formation of channels (40, 42, 46-49, 70-77) between the two Wafern (2, 4), characterized by at least one valve (50; 51; 80; 82) in the region of the Zusammenlaufs of a first channel (46; 48; 76; 74) and a second channel (47; 49; 77; 75) to a third channel (40; 47; 71; 77), and by one as flexible layer of the first or second wafer (2, 4) trained diaphragm (95), the one flexible extent section of the wall of the first channel (46; 48; 76; 74) forms, whereby itself the flexible extent section in closing position of the valve (50; 51; 80; 82) against a opposite firm extent section of the wall of the first channel (46; 48; 76; 74) puts on itself and in Offenstellung of the valve (50; 51; 80; 82) from the firm extent section (97) takes off.
24. Device according to claim 23, characterised in that the firm extent section a collection (97) of the first or second wafer (2, 4) between the recesses for the first channel (46; 48; 76; 74) on the one hand and for second (47; 49; 77; 75) und dritten Kanal (40; 47; 71; 77) on the other hand exhibits, at which the diaphragm (95) in closing position of the valve (50; 51; 80; 82) sealing to the plant comes.

25. Device according to claim 23 or 24, characterized by a pressure chamber (93) on the channel-turned away side of the diaphragm (95), whereby the diaphragm (95) puts on itself on admission of the pressure chamber (93) with an overpressure at the firm extent section and takes off with creation of a vacuum in the pressure chamber (93) from the firm extent section.
26. Device according to claim 25, characterized lidding foil (94), taking off by the pressure chamber (93), which exhibits an opening (96) for the connection of a sucking and/or a pressure pump.